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Published in:
JOURNAL OF CARDIAC FAILURE

DOI:
10.1016/j.cardfail.2009.09.006

Publication date:
2010

The Impact of Perceived Adverse Effects on Medication Changes in Heart Failure Patients

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ABSTRACT

Background: Given the importance of patient safety and well-being, we quantified the likelihood and type of medication changes observed after 5 possible adverse effects (AE) perceived by heart failure (HF) patients.

Methods and Results: We conducted a retrospective cohort study using 18 months follow-up data from the Coordinating study evaluating Outcomes of Advising and Counseling in HF study on 754 patients previously hospitalized for HF (NYHA II-IV, mean age 70 years). Data used for this secondary analysis included problem checklists that patients had completed at 3 points in time, and medication data collected from chart review. Changes in potential causal cardiovascular medication and relevant alleviating medication were classified. Within group and relative risks (RR) for medication changes were calculated. Of the 754 patients, 50% reported dizziness, 44% dry cough, 19% nausea, 19% diarrhea, and 12% gout on the first checklist. Overall, the likelihood of a medication change was increased by 38% after a perceived AE. Dry cough had the highest increased likelihood of an associated cardiovascular medication change (RR 1.83, CI 1.35-2.49). Patients reporting gout had a four fold higher likelihood of alleviating medication started or intensified.

Conclusions: A considerable number of HF patients perceived possible AE. However, the likelihood of medication being changed after a possible AE was rather low. There seems to be room for improving the management of AE. (*J Cardiac Fail 2010;16:135−143*)

Key Words: Cardiovascular disease, adverse drug reactions, risk management, physician-patient relations.

Pharmacological treatment is the cornerstone of heart failure (HF) management, significantly improving morbidity and mortality.[1,2] Although medication is in general beneficial, it has the potential to do harm as well. We previously reported that up to 17% of HF patients may experience (mild) adverse effects of their medication.[3] When patients raise concerns about possible adverse effects, physicians may not actively engage in the discussion, and patients' concerns are not always identified.[4] This may affect the quality of life and patient adherence and increase patients' dissatisfaction with care.[5-7] In addition, the failure to respond to medication related symptoms can also contribute to unnecessary discomfort and harm caused by ameliorable adverse drug events.[8,9] The severity or the duration of such events could be reduced by adequate (re)action.[5]

So far, little information is available about the extent of adequate reaction to possible adverse effects in HF patients. Information about medication changes to stop or ameliorate adverse events is helpful to identify aspects of management in need of improvement.

The objective of this study was to evaluate the impact of perceived adverse effects that can be caused by drugs frequently used in HF patients on the

- likelihood and type of changes of potential causal cardiovascular medication and
- initiation of medication to alleviate the adverse effect.

Methods

Sample and Setting

The current study used secondary data which had been collected in a multicenter randomized controlled trial, the Coordinating

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Manuscript received May 20, 2009; revised manuscript received September 23, 2009; revised manuscript accepted September 24, 2009.

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The COACH study was supported by grant 2000Z003 from the Netherlands Heart Foundation. This study was financed through an Ebbo Emmius scholarship at the University of Groningen, the Netherlands.

1071-9164/$ - see front matter

doi:10.1016/j.cardfail.2009.09.006

Box 1. Definitions of Medication Changes

Medication changes related to causal cardiovascular drugs:
Stop: A medication is considered to be stopped when it is discontinued and not restarted in a maximum period of 6 months (between 2 problem checklists).
Gap: There is a discontinuation in the prescribed medication ranging from a minimum of 2 days to a maximum of 6 months, depending on the dosage at reinitiating (ie, gap with *lower* dosage or a gap with the *same* dosage).
Switch: A new drug is started within 2 days after medication is discontinued. Switching of medication can occur at different levels of the ATC classification for drug treatment. Switch at level 5: a switch between two drugs at the chemical substance level (eg, lisinopril-perindopril).
Switch at level 4: a switch between two drugs at the chemical subgroup level (eg, thiazide-thiazide combination product).
Switch at level 3: a switch between two drugs within the same pharmacological subgroup (eg, ACE-inhibitor to ARB).
Dose decrease: A decrease in the dosage of the same medication.
Medication changes related to alleviating drugs:
Start: A medication is considered to be started when it was not prescribed in a maximum period of 6 months (between 2 problem checklists).
Gap: Conform the *Gap* definition above, except focusing at a gap with a *higher* dosage at reinitiation.
Switch: Conform the *Switch* definition above.
Dose increase: An increase in the dosage of the same medication.
ATC: Anatomical Therapeutic Chemical (ATC); ACE inhibitor: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

study evaluating Outcomes of Advising and Counseling in HF (the COACH study).[10,11] The COACH study was designed to determine the effect of education and counseling in HF patients. All patients were enrolled in the study between October 2002 and February 2005 when they were hospitalized for symptomatic HF (New York Heart Association functional Class [NYHA] II-IV) in 1 of 17 heart failure clinics spread over the Netherlands. To be included, patients needed to be older than 18 years and had to have evidence of structural underlying heart disease. Exclusion criteria were invasive procedures in the months before or planned within 3 months after the baseline, already enrolled in other studies, follow-up treatment at another HF clinic, unable or unwilling to complete questionnaires, or to give informed consent. After giving written informed consent in the COACH study, patients were randomized at discharge (baseline) to either care as usual or to 2 intervention care groups: a basic support group or an intensive support group.

Study Design and Data Collection

We conducted a retrospective cohort study using 18-month follow-up data from the COACH study. For this secondary analysis, we used information from medical charts and questionnaires that patients had completed at month 1, 6, and 12 after discharge from the hospital. The Central Ethics Committee approved the study and the investigation conformed to the principles outlined in the Declaration of Helsinki.

Measures

Perceived Adverse Drug Effects. A checklist of 15 disease- or drug-related symptoms or problems that are often perceived by HF patients was used to collect data on possible adverse effects. The question was phrased as follows: ''Did you experience since the last interview:?'' (list of 15 problems) (yes or no). Of the problems addressed, 5 were possible adverse effects of cardiovascular medication that could be consistently related to pharmacological subgroups of such drugs (see the following section). These were included in our study, and concerned dry or hacking cough (= dry cough), nausea, dizziness, diarrhea, and gout. To separate cough associated with worsening HF from the dry or hacking cough caused by angiotensin-converting enzyme (ACE) inhibitors, coughing in general was not included in our analysis, though it was included as a separate problem in the checklist.

Medication Therapy. All prescribed medication and medication changes were registered during 18 months of follow-up in the electronic patients' charts. We classified medication changes into different types of changes that could be considered as indicated reactions to the perceived adverse drug effects (Box 1). As potential causal drugs, we included all cardiovascular medications (C-group within the Anatomical Therapeutic Chemical classification system), which were prescribed at least once in the included patient cohort (21 drugs). Medications were considered related to 1 or more of the possible adverse effects when that specific adverse effect was mentioned as a pharmacological subgroup effect in the Drug Compendium (Appendix 1).[12] For example, dry cough was considered to be related to ACE inhibitors, whereas dizziness could be related to 18 different subgroups, such as cardiac glycosides, antiarrhythmics (class I and III), or β-blockers. For each of the 5 adverse effects, alleviating medication was defined as any drug that was indicated for that specific problem according to the Drug Compendium (Appendix 1). For example, both nonsteroidal anti-inflammatory drugs (M01A) and antigout preparations (M04A) have gout as an indication, and were therefore included in the analysis.

Demographic and Clinical Variables

Demographic and clinical variables were collected from patient interviews administered at discharge and from the medical charts.

Statistical Analysis

We performed descriptive analysis to calculate the number of perceived possible adverse effects, the percentages of such adverse effects that could be related to concurrently prescribed medication, and related medication changes in the following period of 5 to 6 months. In this way, we limited the period between the perceived problem and the action taken to a maximum of 6 months. Each patient had a maximum of 3 occasions to report a possible adverse effect. Patients who perceived a specific adverse effect were included up to their first report. A separate descriptive analysis was conducted for patients who reported the same adverse effect on all 3 occasions.

We estimated the likelihood of receiving a related medication change in the period after a positive or a negative report of a possible adverse effect by calculating the within group risk (R) and the relative risk (RR) with 95% confidence intervals (CI).

First, we calculated the overall likelihood of receiving a medication change after a perceived adverse effect. For this, we compared patients with and without any report of an adverse effect in the first period regarding all related medication changes. To assess whether medication changes were more likely for HF-specific medication, we performed subanalyses for HF-specific and other cardiovascular medications, including the adverse effects that could be attributed to both groups of medication. Ratio of relative risks (RRR) and test of interaction (z-score) were calculated to

assess significant differences between relative risks of the 2 groups.[13]

Next, the within group risks and RR of receiving a medication change were calculated for each of the 5 adverse effects, looking at discontinuation or lowering of the potential causal drugs as well as at initiation or intensification of drugs to alleviate the specific adverse effect. The risk of a medication change was assessed in patients for the three intervention HF care groups and for the 3 periods of data collection separately, and ratios of relative risks (RRR) were calculated to test for differences. When no significant differences were observed, the groups were pooled for further analysis and the weighted mean of the RR is presented.

Finally, risks and RR were calculated for each of the different types of medication changes (Box 1). Statistical analyses were performed using SPSS 16.0 software (SPSS Inc, Chicago, IL).

Results

Study Population

Of the 1023 HF patients in the COACH study, 754 patients completed the checklist in the first month, and had a follow-up of at least 2 consecutive visits with checklists. The mean age at baseline was 70 years and 37% were female (Table 1). Eighty percent of the HF patients reported 1 or more comorbidities. At discharge, the majority of patients were on diuretics, ACE inhibitors, and β-blockers.

Table 1. Demographic and Clinical Characteristics of the HF Population

	n = 754 % or mean ± SD
Demographics	
Age (y)	70 ± 12
Gender (female)	37
Educational level	
No education/primary school	51
Secondary school	28
Higher education/university	21
Clinical characteristics	
Duration of heart failure (months) − (median)	0.69
LVEF %	34 ± 14
Patients with LVEF <40%	73
NYHA (at discharge)	
II	54
III-IV	46
Ischemic etiology of HF	41
Comorbidities	
No comorbidities	20
Vascular disorders	58
Respiratory disorders (COPD/asthma)	29
Diabetes	27
Medication burden	7.3 ± 2.7
Heart failure medication (at discharge)	
ACE inhibitors	75
ARBs	13
β-blockers	68
Cardiac glycosides	28
Diuretics	96
High-ceiling diuretics	88
Potassium-sparing diuretics	52
Other medication (at discharge)	
Calcium channel blockers	16
Nitrates	31
Lipid-lowering agents	40
Antiplatelet drugs	30
Anticoagulants	61
Antiarrhythmic agents	10
Other antihypertensive medication	2.5

LVEF: left ventricular ejection fraction; NYHA: New York Heart Association classification; COPD: chronic obstructive pulmonary disease; ACE inhibitors: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blocker.

Total Numbers of Perceived Adverse Effects and Medication Changes

Of the 754 patients, 50% reported dizziness, 44% dry cough, 19% nausea, 19% diarrhea, and 12% gout on the first checklist. During the whole study period, 544 patients reported dry cough and 512 dizziness, whereas gout was reported by 156 patients (Table 2). Of the patients reporting dry cough, 74% were on potentially related medication (ACE inhibitors), but only in 19% of the cases this medication was subsequently changed (Table 2). This percentage did not differ for patients reporting dry cough on 3 consecutive occasions. Almost all patients reporting gout, nausea, dizziness, and diarrhea were on prescribed medication that could cause such effects. Those who experienced dizziness showed the highest number of potentially related medication changes (45%). More medication changes were observed in patients reporting dizziness on 3 consecutive occasions. This was also the case for gout, nausea, and diarrhea (Table 2).

Likelihood of Cardiovascular Medication Changes after Adverse Effects

The total estimated relative risk for experiencing a medication change after perceiving a possible adverse effect was 1.38 (CI 1.11-1.71). There was no significant difference between the relative risks (RRR 0.96, $P = .3$) for changing HF-specific medication (RR 1.31, CI 1.11-1.55) and other cardiovascular medication (RR 1.36, CI 0.90-2.05). Also, no significant differences were found between the care as usual group I and the intervention care groups; basic support group II and intensive support group III (RR group I: 1.52, CI 0.95-2.43; group II: 1.11, CI 0.81-1.52; group III: 1.52, CI 1.07-2.15; RRR I vs. II: 1.37, $P = .3$; RRR I vs. III: 1.0 $P = 1.0$; RRR II vs. III: 0.73, $P = 0.2$), nor between the 3 periods of data collection (RR period 1: 1.38, CI 1.11-1.71; period 2: 1.26, CI 1.00-1.58; period 3: 1.62, CI 1.21-2.17, RRR 1 vs. 2: 1.10, $P = .6$; RRR 1 vs. 3: 0.85, $P = .4$; RRR 2 vs. 3: 0.78, $P = .2$). Consequently, the groups as well as the periods were pooled together for all further analyses, and the weighted mean of the RR is presented. The RR per period is presented in Appendices 2 and 3 (see Appendix 2 available on page 141.e2 and Appendix 3 available on page 141.e2 at www.onlinejcf.com).

The risk of a related medication change was significantly increased after perceiving dry cough, nausea, dizziness, or diarrhea with dry cough showing the highest increase in risk of 83% (RR = 1.83, CI 1.35-2.49) (Table 3). In case of gout, no significant increase in cardiovascular medication changes was observed.

Table 2. Total Numbers and Percentages of Perceived Adverse Effects (AE), Related Medication, and Medication Changes after the First Report and after 3 Repeated Reports

AE	Total Number of Reported AE by Unique Patients*	Total % of Related Medication for Reported AE	Total % of Possible Related Medication Changes after Reported AE	Total % of Possible Related Medication Changes after 3 Reports of Same AE
Dry Cough	544	400/544 (74%)	77/400 (19%)	16/84 (19%)
Gout	156	150/156 (96%)	37/150 (25%)	19/41 (46%)
Nausea	259	254/259 (98%)	92/254 (36%)	21/27 (78%)
Dizziness	512	512/512 (100%)	231/512 (45%)	129/165 (78%)
Diarrhea	254	244/254 (96%)	74/244 (30%)	13/29 (45%)

*Total number of reported AE by unique patients during the whole study period.

Likelihood of Medication Changes of Alleviating Drugs after Adverse Effects

Patients perceiving gout had a significant 4-fold higher likelihood of having alleviating medication started or intensified (RR = 4.23, CI 2.23-8.05) (Table 4). For none of the other adverse effects, increased rates of related alleviating medication changes were observed in the follow-up period.

Type of Medication Changes

Figure 1 gives an overview of the relative risks of the different types of medication changes per adverse effect. When dry cough is reported in the checklist, patients had a significant 10-fold increased likelihood of having their ACE inhibitor switched to an ARB (RR = 10.67, CI 3.2-35.55). Patients perceiving gout had a 3-fold higher likelihood that their diuretics were temporarily discontinued and reinitiated at a lower dosage (RR = 3.32, CI 1.09-10.04). For nausea, dizziness, and diarrhea, more diverse types of medication changes were observed, including medication discontinuations and dose decreases.

Discussion

This is the first study that looked at actual medication changes among HF patients who perceived possible adverse effects of their cardiovascular drugs. A considerable number of patients experienced adverse effects, with dry cough and dizziness being common problems. The vast majority (74% to 100%) of these patients received medication known to cause the perceived problems. The likelihood that this medication was subsequently changed was 38% higher than when no such adverse effects were reported, but was not significantly different for HF-specific medication and other cardiovascular medication. This suggests that, although patients are attending a HF clinic, clinicians are not more prone to focus only on HF-specific medication.

The high number of patients experiencing adverse effects, such as dry cough and dizziness, are in agreement with other studies on symptom prevalence in HF.[14,15] The overall likelihood of medication being subsequently changed in our study seems low in comparison to other patient populations; for example, primary care patients of 18 years and older reported more than 75% of medication changes in response to perceived medication symptoms.[16] The lower rates observed in our population of HF patients can be attributed to multiple underlying factors. First, patients may have failed to report the perceived problem to their health care provider. Previous research showed that one third to one half of patients do not spontaneously communicate perceived adverse effects with their physician.[3,17] Patients' involvement and willingness to discuss and communicate health problems is influenced by many factors. The health care setting can play a role, where patients may perceive more difficulties in communicating with hospital staff in comparison with their general practitioner.[18] The professional role of health care staff can also affect the patients' willingness to discuss certain complaints. It was found, for example, that physical complaints were more often communicated to the general practitioner than to the nurse practitioner.[19] Patient-related factors are also important, where elderly patients may consider observed

Table 3. Within Risks and Relative Risks for Medication Changes of Related Cardiovascular Drugs after Perceiving a Specific Adverse Effect (AE)

AE	Total n (with AE and on Medication/Without AE and on Medication)	Within Risk Medication Changes with AE		Within Risk Medication Changes without AE		Relative Risk* (95% CI)
Dry cough	400/610	(77/400)	0.19	(64/610)	0.10	1.83 (1.35-2.49)
Gout	150/1617	(37/150)	0.25	(322/1617)	0.20	1.24 (0.92-1.67)
Nausea	254/1521	(92/254)	0.36	(364/1521)	0.24	1.51 (1.26-1.82)
Dizziness	512/811	(231/512)	0.45	(270/811)	0.33	1.36 (1.18-1.55)
Diarrhea	244/1468	(74/244)	0.30	(285/1468)	0.19	1.56 (1.26-1.94)

*Relative risk is not equal to the deviation of within risk with AE and within risk without AE because of rounding.

Table 4. Within Risks and Relative Risks for Medication Changes of Alleviating Drugs after Perceiving a Specific Adverse Effect (AE)

AE	Total N (with AE/without AE)	Within Risk Medication Changes with AE		Within Risk Medication Changes without AE		Relative Risk* (95% CI)
Dry cough	544/835	7/544	0.01	6/835	0.007	1.79 (0.61-5.30)
Gout	156/1761	12/156	0.08	32/1761	0.02	4.23 (2.23-8.05)
Nausea	259/1538	7/259	0.03	37/1538	0.02	1.12 (0.51-2.49)
Dizziness	512/811	0/512	—	0/811	—	—
Diarrhea	254/1532	0/254	—	0/1532	—	—

*Relative risk is not equal to the deviation of within risk with AE and within risk without AE because of rounding.

symptoms or problems as an unavoidable part of aging.[20] Second, when problems are reported by patients, health care providers may fail to acknowledge the adverse effects or focus mainly on adverse effects which are clinically relevant and necessitate immediate intervention.[20,21] A study on doctors' attitudes revealed that up to 20% of the respondents did not consider medication adverse effects a concern related to clinical practice.[22] During encounters on medication, patients were usually the ones who raised concerns about medication problems such as adverse effects.[4,23] Third, not all perceived problems will actually be caused by related drugs, and patients may misinterpret HF-related symptoms as adverse effects of medication.[24] Although we separated general coughing from dry cough by not including coughing reports in the analyses, it is still possible that some patients may have reported dry cough that was caused by fluid retention instead of ACE inhibitor use. Finally, the low likelihood of medication being changed can partly be explained by a conscious choice not to change the medication. Continuation of medication despite perceiving an adverse effect does not necessarily indicate suboptimal quality of care but can be the result of shared decision-making.[25] After the perceived adverse effect is discussed with the health care professional, patients may decide to accept the adverse effect because the harm does not weigh up against the advantages of the drugs.

Dealing with problems such as dry cough or gout may be more straightforward in comparison to nausea, dizziness, or diarrhea. Nausea and dizziness in particular are symptoms that are difficult to interpret in terms of adverse effects. They occur quite often but can be the result of many medications as well as other factors, such as the disease itself or other related diseases. This complexity may be a barrier to change the medication. At the same time, the high number of medications that can be related to the adverse effect will increase the probability of observing unrelated medication changes. This can be confirmed by our findings showing that nausea and dizziness both had rather low relative risks of related cardiovascular medication changes, despite having the highest absolute numbers of medication changes. Perceiving dry cough, on the other hand, showed a high relative risk for subsequent switches of the ACE inhibitor medication to an ARB. This is in agreement with a survey study among patients with hypertension showing that cough is an adverse effect often mentioned as reason for changing the related treatment.[26] In our study, gout showed no significant increased overall cardiovascular medication changes, but we did observe an increased likelihood of a temporary discontinuation followed by a dose decrease of the related diuretic medication. Also, we observed a large increase in the use of alleviating drugs for gout. Both can be considered adequate actions. Diuretics are first-line drugs in symptomatic HF treatment, and form an essential cornerstone of the drug therapy.[1] Permanent discontinuation will seldom be the preferred option but rather alleviating the gout will be attempted. Alleviating symptoms would also be an indicated response to the other adverse effects, but we did not observe this in our study. The drugs, however, used for alleviating these other adverse effects are mostly over-the-counter drugs in the Netherlands, and may therefore not be well-documented in the patients' charts.

Our study relies on patients' self-reported data using questionnaires with problem checklists that were linked to records of actual medication changes. We focused on 5 possible drug-related adverse effects. We limited the analyses to changes in related medication in the period after a report of a possible adverse effect. We cannot, however, be certain that the reported problems could indeed be attributed to the medication, and that this was acknowledged by the health care provider. By focusing on specific medication changes to stop or alleviate adverse effects, we did not take all possible adequate actions into account that a health care provider might have taken in view of more full knowledge about the (history of the) patient. On the other hand, because of recall bias, patients may not have reported all perceived problems in the questionnaires. Therefore, we may have missed some related medication changes.

A strong point of our study is that we compared medication changes in patients using similar medication with or without perceiving a related problem. This reduces the risk of attributing unrelated medication changes, for example, those caused by efficacy problems, to the perceived adverse effect.[26]

Future research on this topic is needed, including a broader range of possible adverse effects of medication, and a more detailed documentation of other factors such as comedications and comorbidities. For practice but also for research and monitoring purposes, it is important that the discussion or rationales of (not) changing medication in the context of possible adverse effects is consistently documented in patients' charts. This is especially important for patients who are treated by several health care providers over time.

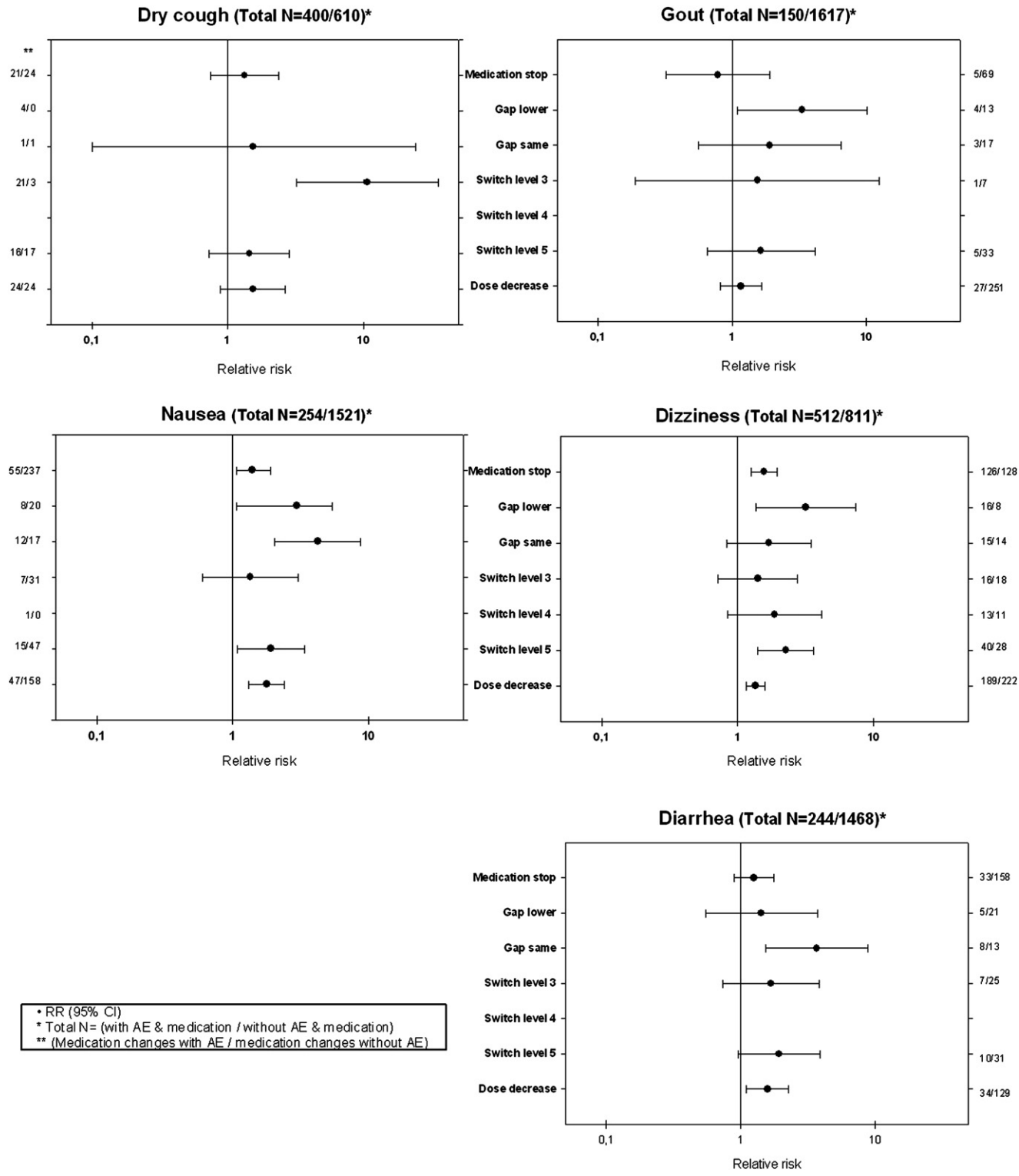

Fig. 1. An overview of the relative risks of the different types of medication changes per adverse effect.

In conclusion, this study reveals a rather low likelihood of medication being changed after patients perceived possible adverse effects of their medication. Given the high number of patients perceiving such problems, which are known to affect quality of life and medication adherence,[5] there is a need for better management. This management should focus on the factors that may underlie the apparent lack of reaction, including the failure of acknowledging and discussing possible adverse effects by both patient and health care professional. Patients preferred to be informed and coached regarding adverse effects of medication.[27] Health care professionals should always consider the possibility

of adverse effects in the differential diagnosis of perceived symptoms in elderly patients.[28] Because patients may not know that the problems are adverse effects that might be alleviated by medication changes, health care professionals should actively elicit perceived adverse effects on a recurrent basis.

Acknowledgments

The authors would like to thank J. Voorham for designing a program to facilitate the evaluation of medication changes.

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Appendix 1

Included Medications

Adverse Effect	ATC Code	Pharmacological Subgroup
Dry cough		
Cardiovascular drugs	C09A	ACE inhibitors, plain
	C09B	ACE inhibitors, combinations
Alleviating drugs	R05C	Expectorants, excluding combinations with cough suppressants
	R05D	Cough suppressants, excluding combinations with expectorants
Gout		
Cardiovascular drugs	C03A	Low-ceiling diuretics, thiazides
	C03B	Low-ceiling diuretics, excluding thiazides
	C03C	High-ceiling diuretics
	C03E	Diuretics and potassium-sparing agents in combinations
	C09B	ACE inhibitors, combinations
	C09D	Angiotensin II antagonists, combinations
Alleviating drugs	M01A	Antiinflammatory and antirheumatic products, nonsteroids
	M04A	Antigout preparations
Dizziness		
Cardiovascular drugs	C01A	Cardiac glycosides
	C01B	Antiarrhythmics, class I and III
	C01D	Vasodilators (used in cardiac diseases)
	C02A	Antiadrenergic agents, centrally acting
	C02C	Antiadrenergic agents, peripherally acting
	C02D	Agents acting on arteriolar smooth muscle
	C03A	Low-ceiling diuretics, thiazides
	C03B	Low-ceiling diuretics, excluding thiazides
	C03C	High-ceiling diuretics
	C03E	Diuretics and potassium-sparing agents in combinations
	C04A	Peripheral vasodilators
	C07A	β-blocking agents
	C08C	Selective calcium channel blockers (vascular effects)
	C08D	Selective calcium channel blockers (cardiac effects)
	C09A/B/C/D	Agents acting on the renin-angiotensin system (excluding C09X)
Alleviating drugs	N07C	Antivertigo preparations
Nausea		
Cardiovascular drugs	C01A/B/C/D	Cardiac therapy (excluding C01E)
	C02A	Antiadrenergic agents, centrally acting
	C02C	Antiadrenergic agents, peripherally acting
	C03D	Potassium-sparing agents
	C03E	Diuretics and potassium-sparing agents in combinations
	C04A	Peripheral vasodilators
	C08C	Selective calcium channel blockers (vascular effects)
	C08D	Selective calcium channel blockers (cardiac effects)
	C09A/B/C/D	Agents acting on the renin-angiotensin system (excluding C09X)
	C10A	Lipid modifying agents, plain
Alleviating drugs	A03F	Propulsives
	H02A	Corticosteroids for systemic use/oral use
	R06A	Antihistamines for systemic use/oral use
	N05A	Antipsychotics
	N07C	Antivertigo preparations
Diarrhea		
Cardiovascular drugs	C01A	Cardiac glycosides
	C03D	Potassium-sparing agents
	C03E	Diuretics and potassium-sparing agents in combinations
	C9A/B/C/D	Agents acting on the renin-angiotensin system (excluding C09X)
Alleviating drugs	A07D	Antipropulsives

ACE: angiotensin-converting enzyme.

Appendix 2

Table 3bis. Within Risks and Relative Risks for Medication Changes of Related Cardiovascular Drugs after Perceiving a Specific Adverse Effect (AE) per Period

AE	Total n (with AE and on medication/without AE and on medication)	Within Risk: Medication Changes with AE	Within Risk: Medication Changes without AE	Relative Risk* (95% CI)
Dry cough: Total	400/610	77/400	64/610	1.83 (1.35-2.49)
Period 1	243/312	51/243	41/312	1.60 (1.10-2.32)
Period 2	112/180	23/112	13/180	2.84 (1.50-5.38)
Period 3	45/118	3/45	10/118	0.79 (0.23-2.73)
Gout: Total	150/1617	37/150	322/1617	1.24 (0.92-1.67)
Period 1	85/620	19/85	153/620	0.91 (0.60-1.38)
Period 2	37/544	10/37	109/544	1.35 (0.77-2.35)
Period 3	28/453	8/28	60/453	2.16 (1.15-4.10)
Nausea: Total	254/1521	92/254	364/1521	1.51 (1.26-1.82)
Period 1	143/604	65/143	191/604	1.44 (1.16-1.78)
Period 2	66/505	18/66	108/505	1.28 (0.83-1.96)
Period 3	45/412	9/45	65/412	1.27 (0.68-2.37)
Dizziness: Total	512/811	231/512	270/811	1.36 (1.18-1.55)
Period 1	379/375	185/379	149/375	1.23 (1.05-1.44)
Period 2	96/254	36/96	87/254	1.09 (0.80-1.49)
Period 3	37/182	10/37	34/182	1.45 (0.79-2.66)
Diarrhea: Total	244/1468	74/244	285/1468	1.56 (1.26-1.94)
Period 1	135/593	46/135	154/593	1.31 (1.00-1.72)
Period 2	70/483	16/70	77/483	1.43 (0.89-2.31)
Period 3	39/392	12/39	54/392	2.23 (1.31-3.80)

*Relative risk is not equal to the deviation of within risk with AE and within risk without AE because of rounding.

Appendix 3

Table 4bis. Within Risks and Relative Risks for Medication Changes of Alleviated Drugs after Perceiving a Specific Adverse Effect (AE) per Per

AE	Total n (with AE/without AE)	Within Risk: Medication Changes with AE	Within Risk: Medication Changes without AE	Relative Risk* (95% CI)
Dry cough: Total	544/835	7/544	6/835	1.79 (0.61-5.30)
Period 1	335/419	5/335	4/419	1.56 (0.42-5.78)
Period 2	143/256	1/143	1/256	1.79 (0.11-28.41)
Period 3	66/160	1/66	1/160	2.42 (0.15-38.19)
Gout: Total	156/1761	12/156	32/1761	4.23 (2.23-8.05)
Period 1	88/666	6/88	13/666	3.49 (1.36-8.96)
Period 2	39/594	1/39	13/594	1.17 (1.16-8.73)
Period 3	29/501	5/29	6/501	14.39 (4.67-44.40)
Nausea: Total	259/1538	7/259	37/1538	1.12 (0.61-2.49)
Period 1	146/608	5/146	14/608	1.49 (0.54-4.06)
Period 2	67/513	2/67	18/513	0.85 (0.20-3.59)
Period 3	46/417	0/46	5/417	—
Dizziness: Total	512/811	0/512	0/811	—
Period 1	379/375	0/379	0/375	—
Period 2	96/254	0/96	0/254	—
Period 3	37/182	0/37	0/182	—
Diarrhea: Total	254/1532	0/254	0/1532	—
Period 1	142/612	0/142	0/612	—
Period 2	73/509	0/73	0/509	—
Period 3	39/411	0/39	0/411	—

*Relative risk is not equal to the deviation of within risk with AE and within risk without AE because of rounding.